

## REMARKS

### In the Claims

Claim 4 is amended to make the claim easier to read.

Claim 6 is amended to expressly recite the host as suggested by the Examiner.

The allegedly indefinite terms are removed from claim 7 and the deleted subject matter of claim 7 is claimed in separate new claim 37.

Claim 8 is amended and the deleted subject matter of claim 8 is claimed in separate new claim 40.

New claims 35 and 36 correspond to claims 1 and 20, respectively, but specify the amino acid derivatives taught on page 8, lines 1-10. Claims 24 and 25, directed to the same subject matter have been cancelled without prejudice or disclaimer.

New claim 38 corresponds to claim 32, but specifies the reactive derivatives taught on page 13, lines 31-35.

New claim 39 corresponds to claim 33, but specifies the functional derivatives taught on page 14, lines 17-38.

New claim 41-46 is added to specify agents which achieve cyclization of compounds of formula III in claims 4 and 32. Support for these new claims can be found, for example, on page 13, lines 14-28.

### The Rejections under 35 U.S.C. § 112, first paragraph

Claims 5-8 and 21 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled by the disclosure.

The arguments with respect to *In re Marzocchi*, *Cross v. Iizuka*, *In re Brana*, *Fujikawa v. Wattanasin*, *Union Oil Co. of California v. Atlantic Richfield Co.*, *In re Angstadt*, *Ex parte Jackson*, *In re Bundy*, appearing in previous replies is incorporated herein by reference. Applicants regret to see that the Examiner impermissibly restricted the holding of each of these cases to its very specific facts and found them inapplicable to the current situation. These cases were not, and are not, so restricted by the Federal Circuit as can be seen from the opinions themselves and the citation of these cases in many later opinions. Applicants disagree with the standard applied in the prosecution of this application as it is clearly contrary to law.

Additionally, Applicants supply several references, which further demonstrate the *in vivo* and *in vitro* efficacy, as well as clinical activity in human patient, of  $\alpha_v$ ,  $\beta_3$ , and  $\beta_5$  antagonists.

Claims 5, 6, and 21 were rejected for being directed to "pharmaceutical composition," on grounds of alleged non-enablement. It is the Examiner's position that these claims should be treated as method claims. Applicant's are not aware of the authority the Examiner is relying on in making this rejection. However, in view of the Federal Circuit's position in *Union Oil Co. of California v. Atlantic Richfield Co.*, 208 F.3d 989 (Fed. Cir. 2000), holding that composition claims cannot embrace only certain uses because otherwise composition claims would impermissibly mutate into method claims, it is clear that rejecting a composition claim, even if it bears the "pharmaceutical" adjective, is impermissible. Nowhere did the Federal Circuit restrict the holding in *Union Oil* to its facts as the Examiner is limiting the holding of said case. Rather, the Federal Circuit broadly held, as discussed above, that composition claims should not be treated as if they were method claims. Until the law specifically directs for a different treatment for "pharmaceutical compositions," pharmaceutical composition claims should be treated as if they are composition claims, and not method claims.

With respect to the Brooks reference, and the allegations regarding reference #24 cited therein (a copy of reference #24 is attached to this Reply), the Office Action alleges that reference #24 is not a reference, but a mere assertion that a paper was presented, and that neither the results obtained, nor the methods used, can be determined. Applicants respectfully point out that the Brooks reference is in a respected scientific publication. The Brooks reference is cited by many later publications as will become evident even from the additional references submitted along with this Reply.

Reference #24 cited in Brooks is itself a paper presented by respectable scientist(s) at a meeting, presumably attended by at least some of skill in the art (as evidenced by its citation in Brooks). The allegations and speculations in the Office Action that the paper is somehow not a reference are without basis in fact. The Examiner provides no reason why he doubts the assertions made by either of these two references.

To answer the Examiner's allegations regarding reference #24, the study was performed on 2100 patients, and the author(s) concluded that: blockade of IIb/IIIa receptors using 7E3-Fab reduced platelet aggregation, 7E3 administration significantly reduced acute events in patients with active thrombotic lesions, and that follow-up patients receiving 7E3 at 6 months in the trial

showed continued benefit in terms of reduction of clinical restenosis. For details of the research study, applicants direct the attention of the Examiner to the attached reference.

The Office Action continues to argue that *in vitro* antagonism of receptors is not "necessarily" indicative of *in vivo* efficacy. However, a showing of a "necessarily" indicative correlation between *in vitro* and *in vivo* results is not the standard for patentability of pharmaceutical inventions. The standard for patenting in the area of pharmacological inventions has been set out by the Federal Circuit and was cited and discussed by Applicants in previous replies. While some unpredictability may exist in the art of treating diseases, this unpredictability does not under the law prevent the issuance of patents for pharmaceutical compositions and methods of treatment. The Federal Circuit in *Fujikawa*, supra, stated that

"all that is required is that the test be reasonably indicative of the desired pharmacological response. ... There must be a sufficient correlation between the tests and the asserted pharmacological activity so as to convince those skilled in the art, to a reasonable probability, that the novel compound will exhibit the asserted pharmacological behavior."

Additionally, in *Cross*, supra, the court stated that

"*in vitro* results with respect to the particular pharmacological activity are generally predictive of *in vivo* tests results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are."

Thus, demonstrating a "necessary" correlation between *in vitro* and *in vivo* results is not required. One of ordinary skill in the art, through routine experimentation, can evaluate the level of efficacy of the compounds according to the invention. An applicant is not required to go through Phase II testing in order to prove utility. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. See *In re Brana*, supra.

The Examiner in response cites several prior art references which deal with receptors to support the allegation that "in general" *in vitro* inhibition or stimulation of receptors leads to unpredictable results *in vivo*. However, as admitted by the Office Action, the receptors of the cited references are not integrin receptors. The extrapolation from specific non-integrin receptors to how receptors generally, and integrin receptors in particular, would behave is not common practice in this area of art. Each prior art reference is very specific to the

receptor(s) it discusses. No reference appears to attempt to make correlations to other receptors. One of skill in the art would thus not make correlations from unrelated receptor references to integrins. Thus, these references are irrelevant.

The Examiner once again discusses some of the *Wands* factors, and characterizes some of the factors contrary to fact and law.

The Office Action alleges that the nature of the art is such that it is "an area of research which might, at some point in the future, result in effective therapeutic methods." Even if true, that is enough to allow the issuance of a patent for inventions in this field. As discussed in previous replies, and briefly above, "the stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." See *Brana*, supra. Thus, Applicants are not required to provide "evidence" for the record that the integrin inhibitors of the invention can be used to treat ill patients to the extent required by the Examiner. Nevertheless, such evidence is provided herewith as will be discussed below.

The Office Action alleges that the relative skill of practitioners in the relevant art is high, i.e.,

"Research experience in both biochemistry and organic chemistry would be required. In addition, since the method claims are drawn to therapeutic methods, clinical experience in each of the following would be required: oncology, immunology, allergies, infectious disease, cardiology and orthopedics."

In view of the laundry list of requirements, there is probably no person of skill in the world who is a practitioner in this field according to the Examiner as few if any person has all the "required" experience. That is not the case as even based on the citations by the Examiner, there is a vast amount of work done in this field by practitioners in this field. While relative skill of in the art may be high, experience in all the alleged "required" fields is not necessary for one to be a practitioner in this field.

With respect to working examples, the law is clear that "direct evidence," as required by the Office Action, that the compounds can be used to treat the claimed diseases is not required.

With respect to the amount of direction or guidance presented, the allegation that "no guidance" is presented is incorrect in view of, for example, the dose regimens disclosed in the specification as discussed in previous replies. Treatment regimens can be determined within the bounds of routine experimentation with respect to each claimed disease. Additionally, the

disclosure of treatment regimens or dosages in pharmaceutical patents is not required by the statutes, the courts, nor the MPEP, as discussed in previous replies.

With respect to the predictability or unpredictability of the prior art, the Office Action's allegation that minor variations in structure yield unpredictable results is based on a reference that allegedly shows that activity of one specific compound is reduced by the substitution of glycine with alanine. However, that reference is specific to one specific compound under one specific set of conditions, and its loss of activity with the substitution of glycine with alanine is irrelevant to the current application. To bolster the unpredictability allegation the Examiner further alleges that issues such as bioavailability, pharmacokinetics, and xenobiotic metabolism will also all change in unpredictable ways with structure of the compounds. Even if true, such is irrelevant to the patentability of pharmaceutical inventions.

Additionally, the Office Action appears to require a "guarantee" of successful treatment. See Office Action page 12, lines 5-7. No such "guarantee" is required by any cited rule of law, case or court. As a side note, such "guarantees" are not even provided with respect to treatment of well-known and easily curable diseases by medical practitioners. The medical and pharmaceutical fields are not fields full of guarantees, and the law does not require them to be.

Additional references submitted with this Reply are discussed next:

Heiken et al.,  *$\beta 3$  Integrin Expression in Melanoma Predicts Subsequent Metastasis*, J. Surg. Res. 63, 169-173 (1996), provides data which "shows that melanoma patients whose primary tumors express  $\beta 3$  integrin are significantly more likely to relapse and die of disease than those patients with  $\beta 3$ -integrin-negative tumors." See page 171, column 1. The reference discusses the role of  $\beta$  subunits and teaches therein that  $\beta 3$  subfamily is known to be important in endothelial cell migration and vascular biology, and was shown to be critical for tumor angiogenesis. See page 169, second column, and references 17, 21, 22, 25, and 28. Discussion of references 6-10 and 30-33 reveals that "both in vitro and in vivo studies of murine and human melanoma cell lines have shown that  $\beta 3$  integrins are involved in melanoma tumor regression." See page 169, second column. The reference also teaches that " $\alpha_v\beta_3$  integrin is required for tumor angiogenesis and that tumor growth may be abrogated by involution of tumor angiogenesis with  $\alpha_v\beta_3$  inhibition in vitro." See page 170, first column, and references 17 and 28. The authors of the reference indicate that their data suggests new perspectives for designing melanoma therapy

and may yield new therapeutic strategies and prognostic information. See last paragraph of reference.

Gutheil et al., *Targeted Antiangiogenic Therapy for Cancer Using Vitaxin: A Humanized Monoclonal Antibody to the Integrin  $\alpha_v\beta_3$* , Clinical Cancer Research, Vol. 6., 3056-3061, (2002), reports the use of targeted antiangiogenic therapy for cancer in patients with late stage cancer by reporting a phase I study using Vitaxin in humans with cancer. Vitaxin is a humanized monoclonal antibody to the integrin  $\alpha_v\beta_3$ . See page 3056, abstract, and page 3060, first column. The reference teaches that "many disease states (cancer, psoriasis, rheumatoid arthritis, and diabetic retinopathy) are mediated, in part by a pathological angiogenic response. See page 3056, column 2, and references 1-4. The reference also reports that some angiogenic inhibitors have been shown to possess promising antitumor effects." See page 3056, column 2, and references 4, 9, 10. Gutheil also teaches on page 3056, column 2, that there is evidence that indicates that  $\alpha_v\beta_3$  plays a role in the process of inhibiting the adhesive interaction required by angiogenesis vascular endothelial cells (see reference 12) and that in various animal models, antagonists of  $\alpha_v\beta_3$ , such as the  $\alpha_v\beta_3$  specific antibody, LM609, have been shown to decrease angiogenesis and induce tumor regression (see reference 3) or improve arthritic disease (see reference 13). Also,  $\alpha_v\beta_3$  is known to be associated with the induction of apoptosis within the angiogenic blood vessels (see references 4 and 13).

Vitaxin is a humanized version of the LM609 monoclonal antibody that functionally blocks the  $\alpha_v\beta_3$  integrin. This antibody has been shown to target angiogenic blood vessels, see reference 11, and cause suppression of tumor growth in various animal models, see reference 9. Thus, clinical trials were initiated to evaluate the safety and pharmacokinetics of Vitaxin in late stage cancer patients. See paragraph starting on page 3056 and ending on 3057.

To eliminate possible doubt that the patients were really sick, Applicants point to page 3057 discussing the state of the patients as having advanced stage IV, incurable malignancies refractory to standard therapy. Additional information on the patients can be found on the cited page. The patients were not permitted to undergo concomitant treatment with other investigational drugs. See page 3057. The clinical results indicated that after week 9, "seven patients were shown to have at least stable disease in their indicator lesions. One patient ... with a widely disseminated leiomyosarcoma achieved a partial response (45% of baseline) based on assessment of his measurable disease." See page 3059, first column. For one of the patients,

treatment with Vitaxin continued for 93 weeks “based on the impression that Vitaxin was controlling a subset of the patient’s metastatic disease.” See page 3059, second column. For another patient, the tumor growth rate during treatment with Vitaxin appeared to be less than expected. And for yet another patient, the tumor demonstrated a modest decrease in volume. See page 3060, first column. In sum, “of 14 evaluable patients, 8 either demonstrated disease stabilization or a partial response. ... In one patient, treatment resulted in a partial tumor response that was maintained for 22 months. In another patient, slight tumor shrinkage was noted only after the first cycle of therapy.” See page 3060, first column. The authors of the reference conclude that the findings “support the notion that targeting of the vascular  $\alpha_v\beta_3$  integrin may provide clinical benefit to patients with various tumor types without causing significant side effects.” See page 3060, first column.

Trickha et al., *Multiple Roles for Platelet GPIIb/IIIa and  $\alpha_v\beta_3$  Integrins in Tumor Growth, Angiogenesis, and Metastasis*, Cancer Research 62, 2824-2833, (2002), reports that blockade of GPIIb/IIIa and  $\alpha_v\beta_3$  affords significant antiangiogenic and antitumor benefit. See abstract on page 2824. Both *in vitro* and *in vivo* tests were performed.

“In an *in vitro* angiogenesis assay, c7E3 Fab inhibited basic fibroblasts growth factor and platelet stimulated capillary formation of HUVECs ( $IC_{50} = 10 \mu\text{g/ml}$  and  $15 \mu\text{g/ml}$ , respectively), demonstrating that endothelial  $\alpha_v\beta_3$  is important for sprouting, and platelet-stimulated sprouting is mediated by GPIIb/IIIa. In an experimental metastasis assay, a single pretreatment of human melanoma cells with c7E3 Fab ( $2.5 \mu\text{g/ml}$ ) inhibited lung colonization of the tumor cells in severe combined immunodeficient mice. *In vivo*, m7E3 F(ab')<sub>2</sub> partially inhibited growth of human melanoma tumors in nude mice compared with control-treated animals.”

See abstract on page 2824. For details of the study see pages 2825-2831. The reference teaches that several studies have defined the role of integrins in the angiogenic process, see page 2824, column 2, and references 4-6, and that “an antagonist of  $\alpha_v\beta_3$ , LM609, suppressed angiogenesis and blocked growth of human tumors that did not express this receptor.” See page 2824, column 2, and reference 7. The authors state that c7E3 Fab is an “agent that can antagonize GPIIb/IIIa and  $\alpha_v\beta_3$ , and it is widely used in the clinic as an antithrombotic agent,” and that the results of the study reported by authors indicates that “(c)7E3 Fab and murine (m) 7E3 F(ab')<sub>2</sub>, in addition to having antithrombotic effect, also possess antiangiogenic and antitumor properties.” See page 2825, column 1. References 9 and 10 reports that  $\alpha_v\beta_3$  participates in cell adhesion, migration,

invasion, and increase in  $\beta_3$  integrin inversely correlates with survival of melanoma patients. Trickha concluded that  $\alpha_v\beta_3$  participates in angiogenesis, tumor growth and metastasis. See page 2831, column 2. Additionally, the authors found that (c)7E3 Fab “completely” inhibited  $\alpha_v\beta_3$ -mediated human melanoma cell adhesion, spreading, and invasion and that (m) 7E3 F(ab')<sub>2</sub> has direct antitumor activity in vivo, i.e., in nude mice. See page 1832, second column.

Mousa, *Anti-integrin as novel drug-discovery targets: potential therapeutic and diagnostic applications*, Next Generation Therapeutics, Current Opinion in Chem. Biol., 6:534-541, (2002), reports on the potential role of platelets GPIIb/IIIa ( $\alpha_{IIb}\beta_3$ ) integrin in the prevention, treatment and diagnosis of various thromboembolic disorders. See abstract on page 534. The reference teaches that integrins have a role in

“various pathological processes (including angiogenesis, thrombosis, apoptosis and cell migration and proliferation), leading to both acute and chronic disease states (e.g. ocular diseases, metastasis, unstable angina, myocardial infarction, stroke, osteoporosis, a wide range of inflammatory diseases, vascular remodeling and neurodegenerative disorders).”

See abstract on page 534. The reference teaches that “blockade of fibrinogen-binding to the extracellular face of  $\alpha_{IIb}\beta_3$  has been shown to prevent platelet-rich arterial thrombi after coronary angioplasty in myocardial infarction and unstable angina patients.” See page 534, second column, and references 12-14. The reference in table 1 on page 537 teaches that  $\alpha_v\beta_3$  has potential implications in angiogenesis, restenosis, vascular disorders, and osteoporosis, and that  $\alpha_v\beta_5$  has potential implications in angiogenesis and vascular disorders. The reference teaches that “specific matrix proteins via selected integrins and especially  $\alpha_v\beta_3$  may be important targets for selective antagonists aimed at blocking the pathological processes of restenosis.” See page 537, first column, and references 37 and 38.

The reference reviews a large amount of previous work done by others in the art on pages 537 to 538, including the Brooks reference, leading up to the conclusion that “7E3, a function-blocking anti-integrin  $\beta_3$  antibody that recognizes  $\alpha_v\beta_3$  as well as platelet integrin  $\alpha_{IIb}\beta_3$  was recently approved for use in treatment of high-risk angioplasty.” See page 538, second column. Mousa teaches that “inhibitors of  $\alpha_v\beta_3$  promote selective apoptosis of newly sprouting blood vessels, preventing their maturation, ... indicat[ing] that antibody or peptide antagonist of integrins  $\alpha_v\beta_3$  may have a profound therapeutic value in the treatment of diseases associated with angiogenesis.” See page 537, second column, and references 49 and 50. The reference also

discusses that *in vitro* data, as well as data on rats, has demonstrated the potential role of  $\alpha_v\beta_3$  antagonists in osteoporosis, see page 538, second column, and discussed both *in vitro* and *in vivo* data on integrin matrix interactions in vascular injury. The author lists several  $\alpha_v\beta_3$  antagonists under preclinical investigation, including, "Vitaxin [discussed earlier in Gutheil et al.], humanized Mab of LM609, small molecule  $\alpha_v\beta_3$  antagonists from various companies as anti-angiogenic agent in tumor metastasis or ocular meovascularization-mediated disorders such as diabetic retinopathy, in osteoporosis and restenosis post-coronary artery interventions." See page 538, second column. The reference also teaches that several potent small-molecule  $\alpha_v\beta_3$  antagonists are under preclinical investigations for various angiogenesis or vascular-mediated disorders. See page 538, second column. The reference also reports that a humanized form of the antibody LM609 has entered phase II clinical trials and the first of the cyclic peptide antagonists are in initial clinical developments. See page 539, first column.

Additionally, Vitaxin according to a search in the IDDB database, is under development by Medimmune which has commenced phase II trials for the potential treatment of leiomyosarcome also, Vitaxin is in phase I trials for anti-inflammatory treatments and potential rheumatoid arthritis therapy.

Raguse et al., *Cilengitide (EMD 121974) arrests the growth of a heavily pretreated highly vascularized head and neck tumor*, a Clinical Case Report, discusses a clinical case that demonstrates the clinical efficacy of the antiangiogenic agent cilengitide, which is a cyclopeptide and an  $\alpha_v\beta_3$  antagonist according to the present invention, in combination with gemcitabine, in inhibiting rapid tumor growth of a highly vascularized tumor. See page 2. The reference on pages 3-4 discusses the Brooks paper discussed above and discusses other work by Brooks including work on EMD 121974, i.e., Cilengitide, which is currently undergoing clinical trials. The report teaches that the therapy lead to partial remission which resulted in a clinical improvement in the ability of the patient to eat and smell. The patient remained stable for 12 months on maintenance therapy with no tendency towards spontaneous bleeding. See page 5. The report confirms the clinical relevance of targeted antiangiogenic therapy. The authors are optimistic that their findings may lead to new therapeutic treatments strategies. See page 6. The clinical case report was presented during the AACR Meeting "Angiogenesis and Cancer," Oct. 11-15, 2000, Traverse City, Michigan, and meanwhile submitted for publication, however not yet published.

Additionally attached is a pharmacological report, i.e., *in vitro* assay, on the IC<sub>50</sub> values of cyclo-(Arg-Gly-Asp-Dphe-NMeVal), i.e., of Cilengitide, as an  $\alpha_v\beta_3$  and  $\alpha_v\beta_5$  antagonist. The results show IC<sub>50</sub> values in the nanomolar range.

In view of the vast amount of work done on integrin antagonists both *in vitro* and *in vivo* as well as clinical trials on humans of a compound according to the present invention, Applicant(s) submit that the presently claimed integrin inhibitors, which were shown in the Declaration dated June 1, 2001, and filed on July 30, 2001, to inhibit integrins  $\alpha_v\beta_3$  are enabled.

#### **The Rejections under 35 USC § 112, second paragraph**

The Office Action alleges that claims 4-5, and 32-34 are indefinite because they fail to recite an isolation step for the final product. Applicants respectfully disagree. For one of skill in the art to be in possession of a compound or to prepare a compound, he/she does not have to isolate the same. While the claims do not preclude an isolation step, they do not require the same. One of skill in the art may not have to isolate a compound from its reaction medium in order to use it, or in some cases, it may be uneconomical to do so even if the isolated product is more desirable than the one present in the reaction medium. Having claims requiring an isolation step would enable competitors to prepare compounds of the invention by the claimed methods without infringing them merely because a compound of the claimed invention has not been isolated.

Claim 6 is amended to specify the target of administration. The rejection over the term "at least one excipient" seems nonsensical. How one is to determine whether one or ten excipients are present is completely irrelevant to determine the scope of this claim since both one or ten excipients fall within the scope of "at least one excipient." Additionally, one of skill in the art readily understands what is an excipient, and thus understands what is at least one excipient.

The allegedly indefinite subject matter of claim 7 is now in claim 37. Applicants respectfully disagree with the indefiniteness rejection. The rejection is merely to the scope of the claim and not to whether the claim is indefinite or not. One of skill in the art understand the meaning of "coronary heart disease," for example. The Examiner even provided a list of definite diseases which would be understood by one of skill in the art to be coronary heart diseases. Why

would the broader term be indefinite when those of skill in the art are capable of naming definite specific diseases when confronted with the term?

Claims 7-8 are rejected for not reciting that the time and conditions of the administration. Stating the time and conditions is not necessary for the claim to be definite. One of skill in the art is capable of determining the scope of the claim without the recitation of time and conditions of treatment.

Claim 8 is rejected as allegedly indefinite for not specifying how far "upstream" or "downstream" can one go in deciding whether the process is "supported or propagated" by angiogenesis. Applicants are unsure of what the rejection means. Claim 8 is directed to a process of either supporting or propagating angiogenesis. In any event, newly entered claim 40 recites the propagation of angiogenesis, while claim 8 recites the support of angiogenesis.

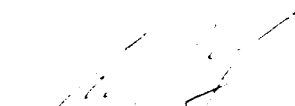
Claims 1 and 20 were rejected for the recitation of "derivatives," claim 32 was rejected for the recitation of "reactive derivative," and claim 33 was rejected for the recitation of "functional derivative." New claims 35 and 36 correspond to claims 1 and 20, but specify the amino acid derivative, new claim 38 corresponds to claim 32, but specifies the reactive derivative, and new claim 39 corresponds to claim 33, but specifies the functional derivative. With respect to the claims that do retain the rejected terms, it is submitted that one of skill in the art could clearly ascertain the scope and meaning of the terms in view of their context and in view of the specification. The term "derivative" is not indefinite where one of ordinary skill in the art can ascertain the term's meaning.

Claim 32 is also rejected as allegedly indefinite for the recitation of the term "an agent suitable to achieve cyclization." The term is clear and definite. The Office Action inquires as to what reagent might be used to achieve cyclization. Thus, the rejection is not over the definiteness of the term, but rather over its breadth, since the meaning is clearly conveyed. The mere breadth of a claim, however, is not grounds for rejecting the same as indefinite.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version With Markings To Show Changes Made**".

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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CH/BPH(pdr) K:\MERCK\2075\REPLY DEC 2002.DOC

Version With Markings To Show Changes Made

In the Claims

The claims have been amended as follows:

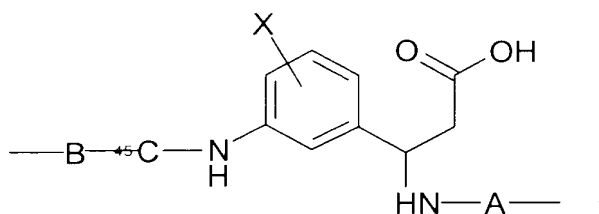
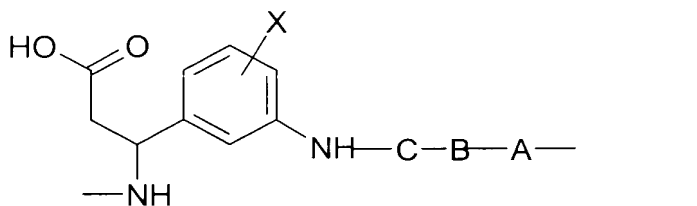
4. (Amended) A process for preparing a compound according to Claim 1 comprising treating a compound of formula III with an agent suitable to achieve cyclization a compound of formula III

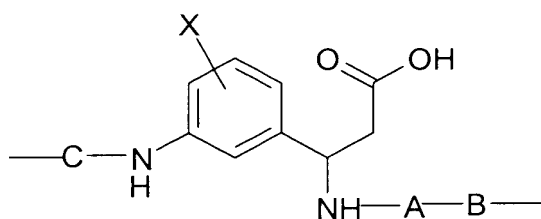
H-Z-OH

III

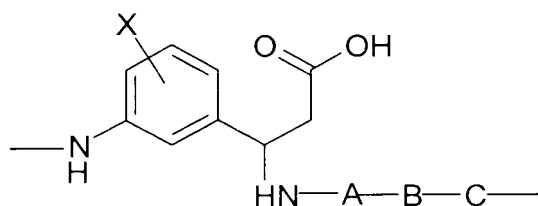
in which

Z is





or



and X, A, B and C have the meanings indicated in Claim 1 for a time and under conditions effective to obtain a compound according to claim 1.

6. (Amended) A pharmaceutical composition comprising at least one compound according to Claim 1, and at least one excipient suitable for sustained administration, parenteral administration, topical application, or administration by inhalation spray to a patient in need thereof.

7. (Amended) A method for the treatment of ~~diseases of the circulation,~~ thromboses, cardiac infarct, ~~coronary heart diseases,~~ arteriosclerosis, apoplexy, angina pectoris, tumours, osteoporosis, inflammations, infections or restenosis after angioplasty, comprising administering to a patient in need thereof an integrin inhibitory effective amount of a compound according to claim 1.

8. (Amended) A method for treating a pathological process that is supported ~~or propagated~~ by angiogenesis, comprising administering to a patient in need thereof of an effective amount of a compound according to claim 1.

**Claims 24 and 25 have been canceled without prejudice or disclaimer.**

**Claims 35-46 have been newly added.**